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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/995,529	WATKINS ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *89-120* is/are pending in the application.

4a) Of the above claim(s) *101-120* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *89-100* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed June 14, 2006, is acknowledged and has been entered. Claims 2-22, 42-63, and 84-88 has been canceled. Claims 89 and 90 have been amended. Claims 91-120 have been added.

2. Claims 89-120 are pending in the application. Claims 101-120 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention or species of invention, there being no allowable generic or linking claim.

3. Claims 89-100 are currently under prosecution.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

5. Newly submitted claims 101-120 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Claims 101-120 are directed to the subject matter of non-elected inventions, which were restricted from the elected invention in accordance with the Office action mailed October 21, 2003.

Since Applicants have received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for further prosecution on the merits. Claims 101-120 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR § 1.142(b) and MPEP § 821.03.

6. Applicant's request for rejoinder at page 15 the amendment filed June 14, 2006, is acknowledged.

All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Grounds of Rejection Withdrawn

7. Unless specifically reiterated below, the amendments and/or arguments accompanying the amendments filed June 14, 2006, have obviated or rendered moot the grounds of rejection of claims set forth in the previous Office action mailed December 30, 2005.

Grounds of Rejection Maintained

Claim Rejections – 35 USC § 112

8. The rejection of claims 89-100 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** an antibody, or a functional fragment thereof, which has at least a two-fold higher binding activity for denatured collagen over native collagen, wherein said antibody or functional fragment comprises

the three heavy chain complementarity determining regions (CDRs) of SEQ ID NO: 46, SEQ ID NO: 28, and SEQ ID NO: 63 and wherein said antibody or functional fragment comprises the three light chain CDRs of SEQ ID NO: 20, SEQ ID NO: 22, and SEQ ID NO: 77, and a nucleic acid molecule encoding said antibody, **does not reasonably provide enablement for making and using** an antibody or a functional fragment thereof that has at least a two-fold higher binding activity for denatured collagen over native collagen, wherein said antibody or functional fragment comprises the three heavy chain CDRs of SEQ ID NO: 45, SEQ ID NO: 155, and SEQ ID NO: 63 and wherein said antibody or functional fragment comprises the three light chain CDRs of SEQ ID NO: 157, SEQ ID NO: 22, and SEQ ID NO: 77, or any other variant of monoclonal antibody HUIV26, which is encompassed by the generic claims, or any nucleic acid molecule encoding said antibody or other variant, is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Beginning at page 15 of the amendment filed June 14, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant's remarks addressing the standard used to determine if the disclosure reasonably enables the skilled artisan to make and use the claimed invention, as required under 35 U.S.C. § 112, first paragraph, are acknowledged. However, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), it is has been determined the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would be insufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

None of claims 89, 90, and 95-100 recite a limitation requiring the members of the genus to have any particular binding activity. Given the broadest, reasonable interpretation that is consistent with the disclosure and that of the skilled artisan, the

claims are directed to a genus of functionally different antibodies. At best, the specification should only be considered reasonably enabling for members of the claimed genus of antibodies that have or retain the binding specificity of the disclosed antibodies (e.g., monoclonal antibody HUIV26), which binds denatured collagen. If members of the claimed genus do not have or retain such binding activity, undue and unreasonable experimentation would be required to use the invention, as it would be necessary to determine the antigen to which such functionally different antibodies bind before they could be used.

Presently, claims 91 and 93, which depend from claim 89 and 90, respectively, are directed to members of the genus of antibodies or functional fragments thereof, which have specific binding activity for "a cryptic collagen epitope".

At paragraph [0036] of the published application[1], for example, the specification defines the term "a cryptic collage epitope" as meaning: "an epitope of a collagen molecule that is less accessible to binding of an antibody, or functional fragment thereof, in native collagen than in denatured collagen". At paragraph [0036], the specification continues, disclosing the following:

> An antibody having binding activity for a cryptic collagen epitope preferentially recognizes denatured collagen over native collagen, that is, has a higher binding affinity for denatured over native collagen". For example, such an antibody can have at least about a 2-fold or greater preference, that is, at least about 2-fold higher binding activity, for denatured collage over native collagen, and can exhibit about a 3-fold or greater preference, about a 5-fold or greater preference, about a 10-fold or greater preference, about a 15-fold or greater preference, about a 20-fold or greater preference, about a 25-fold or greater preference, about a 50-fold or greater preference, about a 100-fold or greater preference, or even a higher preference for denatured over native collagen.

Accordingly, claims 91 and 93 are directed to members of the genus of antibodies or functional fragments thereof, which have at least a two-fold higher binding activity for denatured collagen over native collagen; and claims 92 and 94, which depend from claim 89 and 90, respectively, are specifically directed to these members of the genus of antibodies or functional fragments thereof, which have at least a two-fold higher binding activity for denatured collagen over native collagen.

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[1] U.S. Patent Application Publication No. 2003/0099655 A1.

Again, the elected species of the claimed invention is the antibody, or functional fragment thereof, which comprises the three heavy chain complementarity determining regions (CDRs) of SEQ ID NO: 45, SEQ ID NO: 155, and SEQ ID NO: 63 and the three light chain CDRs of SEQ ID NO: 157, SEQ ID NO: 22, and SEQ ID NO: 77.

As explained in the preceding Office action, the specification teaches two variants of monoclonal antibody HUIV26, which have the requisite preferential binding activity for denatured collagen over native collagen, namely "2D4H1-C3" and "DhuG5"; see, e.g., Figure 8.

However, the specification teaches monoclonal antibody HUIV26 lacks this preferential binding activity, as it does not bind with any substantially greater affinity to denatured collagen over native collagen.

Accordingly, it is evident that the structural variation (i.e. amino acid substitutions), which characterizes the variants, must account for the differential binding activity of the variants as compared to monoclonal antibody HUIV26.

The first of the variants of monoclonal antibody HUIV26, which has the requisite preferential binding activity for denatured collagen over native collagen, namely "2D4H1-C3" comprises a heavy chain variable region comprising the first, second, and third CDRs of SEQ ID NO: 46, SEQ ID NO: 28, AND SEQ ID NO: 63, respectively, and a light chain variable region comprising the first, second, and third CDRs of SEQ ID NO: 20, SEQ ID NO: 22, and SEQ ID NO: 77.

The specification does not, however, describe the particular structure of the other disclosed variant (i.e.,"DhuG5") of monoclonal antibody HUIV26, which allegedly has the requisite preferential binding activity for denatured collagen over native collagen. The disclosure therefore would not enable one skilled in the art to make this variant, and it cannot be ascertained which, if any, of the disclosed amino acid sequences represent its CDRs.

Consequently, the only variant demonstrated to have the requisite preferential binding activity for denatured collagen over native collagen, *which could be made*, is that designated "2D4H1-C3".

As also noted in the preceding Office action, the specification does not provide any showing that the elected species of antibody (i.e., the antibody, or functional fragment thereof, which comprises the three heavy chain complementarity determining regions (CDRs) of SEQ ID NO: 38, SEQ ID NO: 40, and SEQ ID NO: 103 and the three light chain CDRs of SEQ ID NO: 32, SEQ ID NO: 34, and SEQ ID NO: 36) has at least 2-fold greater binding activity for denatured collagen, as compared to its binding activity for native (non-denatured) collagen.

Although the elected species of antibody comprises a heavy chain variable region comprising the same third CDR as the variant designated "2D4H1-C3", which has the requisite preferential binding activity for denatured collagen, *the heavy chain of the elected species of antibody comprises a different first and second CDR* (i.e., a CDR1 having the amino acid sequence set forth as SEQ ID NO: 45, as opposed to the amino acid sequence of SEQ ID NO: 46, and a CDR2 having the amino acid sequence set forth as SEQ ID NO: 155, as opposed to the amino acid sequence of SEQ ID NO: 28). Furthermore, although the elected species of antibody comprises a light chain variable region comprising the same second and third CDRs as the variant designated "2D4H1-C3", *the light chain comprises a different first CDR* (i.e., a CDR1 having the amino acid sequence set forth as SEQ ID NO: 157, as opposed to the amino acid sequence of SEQ ID NO: 20).

The only structurally different features that might account for any differential binding activity, as compared to monoclonal antibody HUIV26, which is shared by the variant designated "2D4H1-C3" and the elected species of invention is the identity of the third CDR of the heavy chain and the identity of the third CDR of the light chain. While it would be understood that that variation in one or both of the first and third CDRs of the heavy chain and/or the variation in the third CDR of the light chain of the variant designated "2D4H1-C3" must account for the observed differential binding activity of the variant, as compared to monoclonal antibody HUIV26 (see, e.g., Figure 8), it is not known, and cannot be predicted whether the variation in the third CDR of the heavy chain alone might account for this differential binding activity.

For this reason, it is not known, and cannot be predicted whether the elected species of invention will also have such preferential binding activity for denatured collagen over native collagen, as compared to monoclonal antibody HUIV26, which does not have such preferential binding activity.

Moreover, it cannot be predicted whether any of the other disclosed variants of monoclonal antibody "2D4H1-C3" have at least 2-fold greater binding activity for denatured collagen, relative to its binding activity for native collagen; for this reason, the claimed invention cannot be made and/or used without undue and/or unreasonable experimentation because it would be necessary to first make a variant of monoclonal antibody HUIV26, which might be encompassed by the claims, and then empirically determine whether it has the requisite binding activity.

Thus, while the skilled artisan has an understanding of the structural basis of antigen-antibody recognition and conventional methodology for humanizing monoclonal antibodies, it is aptly noted that the art is nevertheless characterized by a high level of unpredictability, since the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions, insertions, and deletions in the antigen-binding domains (particularly, within the complementarity determining regions (CDRs)) and surrounding framework regions of antibodies.

This position is supported by references cited in the preceding Office action: Giusti et al. (*Proc. Natl. Acad. Sci. USA.* 1987 May; **84** (9): 2926-2930); Chien et al. (*Proc. Natl. Acad. Sci. USA.* 1989 Jul; **86** (14): 5532-5536); and Caldas et al. (*Mol. Immunol.* 2003 May; **39** (15): 941-952).

As a consequence of the lack of predictability in the art of antibody engineering, it is evident that undue and/or unreasonable experimentation would have to be performed before the claimed invention, reasonably commensurate in scope with the claims, could be made and/or used successfully by the skilled artisan, since, as evidenced by Caldas et al., for example, the skilled artisan cannot reliably and accurately predict the consequences of amino acid substitutions, insertions and deletions in the CDRs of monoclonal antibody HUIV26 upon the structure and function of an antibody comprising such altered heavy and light chain variable regions. Given the teachings of Giusti et al.

(cited *supra*), for further exemplification, it is apparent that even a single amino acid substitution in the primary structure of the heavy chain variable region of an antibody can change both the affinity and specificity of the antibody.

Moreover, although it may be well within the skill of the artisan to graft the three CDRs from both the light and heavy chain variable regions of the disclosed variant of monoclonal antibody designated "2D4H1-C3", which has the requisite binding activity, into the framework of, e.g., a human antibody without substantial loss of that requisite affinity and specificity, the claims are not limited to such engineered antibodies, since the claims are directed to a far broader genus of structurally different antibodies, or functional fragments thereof, having one or more amino acid substitutions within the CDRs if such a variant. Again, as evidenced by Caldas et al. (*supra*), for example, the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions within the antigen-binding domains of an antibody, or more particularly within the CDRs.

As also explained in the preceding Office action, the specification discloses in the table set forth as Figure 4C the amino acid substitutions that were found to be "beneficial" following the introduction of random mutations in the CDRs of either the light or heavy chain variable regions of the Fab of monoclonal antibody HUIV26 (i.e., "wild-type Fab"). The specification discloses such "beneficial" mutations are those producing antibodies binding denatured collagen with higher affinity, relative to the corresponding wild-type Fab, as demonstrated by ELISA; see, e.g., page 87, lines 12-15. The table, for example, indicates that certain substitutions of the amino acid at position 35 of the first CDR of the heavy chain polypeptide of monoclonal antibody HUIV26 (i.e., the amino acid at position 10 within the amino acid sequence of the CDR set forth as SEQ ID NO: 26) are "beneficial", such as the replacement of the naturally occurring serine at this position by threonine, alanine or glycine. In comparison, the claims are directed to a genus of variants of monoclonal antibody HUIV26, which includes but are not limited to a variant comprising a heavy chain comprising a first CDR having the amino acid sequence set forth as SEQ ID NO: 45 (i.e., a heavy chain CDR1 having the amino acid sequence of SEQ ID NO: 26 but for substitution of the amino acid at position 10 by

threonine), as the claims also encompass variants comprising a heavy chain comprising a first CDR having the amino acid sequence of SEQ ID NO: 26 but for substitution of the naturally occurring serine at position 10 by "any conservative substitution" of serine. As disclosed by the specification at page 21, lines 24-31, *exemplary* conservative substitutions of serine include cysteine, methionine, threonine, asparagine, and glutamine. As such, it is duly noted that substitution of the serine at position 35 within the first CDR of the heavy chain of wild-type Fab (i.e., position 10 of CDR1 having the amino acid sequence set forth as SEQ ID NO: 26) by glycine, which is disclosed as a "beneficial" mutation, might not be considered a conservative substitution. Similarly substitution of the amino acid at position 34 of the first CDR (i.e., a methionine, which occurs at position 9 of SEQ ID NO: 26) by isoleucine, which according to the table of Figure 4C is also a "beneficial" mutation, would not ordinarily be considered a conservative substitution, given the fact that substitutions by amino acids having different chemical properties are not generally regarded as "conservative". The different chemical properties of methionine and isoleucine are evident in view of the disclosure at page 21, lines 24-31, that methionine is a "polar" amino acid, whereas isoleucine is "non-polar". Despite the fact that this "beneficial" substitution of the methionine at this position or the "beneficial" substitution of the serine at position 35 by glycine within the first CDR of the heavy chain is not conservative, per se, the claims are directed to a genus of antibodies having a heavy chain comprising a first CDR having the amino acid sequence of SEQ ID NO: 38 but for substitution of the naturally occurring methionine or serine at positions 6 and/or 7 by "any conservative substitution" of methionine and serine, respectively; and yet there is insufficient factual evidence of record that would support the assertion that such substitutions of this methionine or this serine would be found "beneficial", or produce an antibody having the requisite binding activity for denatured collagen over native collagen, as compared to wild-type Fab. To the contrary, there appears to be factual basis for concluding that *non-conservative* substitutions of this methionine by isoleucine and *non-conservative* substitutions of this serine by glycine produce a variant of monoclonal antibody HUIV26 having higher affinity, relative to the corresponding wild-type Fab, as demonstrated by ELISA. These

results underscore the unpredictable nature of the art of antibody engineering that has been shown by the disclosures of Giusti et al, Chien et al., and Calabas et al. (all cited *supra*).

In addition, as also previously noted, according to the table set forth as Figure 6, only certain "combinatorial mutants", which are variants of wild-type Fab (i.e., the Fab of monoclonal antibody HUIV26) comprising more than one of the "beneficial" substitutions identified by random mutagenesis, are disclosed as having equivalent or enhanced binding activity, as compared to wild-type Fab. None of these "combinatorial mutants" however appear to be disclosed as having, per se, at least 2-fold greater binding activity for denatured collagen over native collagen. Furthermore, as the "combinatorial mutants" disclosed in Figure 6 as having equivalent or enhanced binding activity comprise only the one or two substitutions in one or more of the CDRs of the light and/or heavy chain variable regions of monoclonal antibody HUIV26, which are specifically iterated in the claims, it is not known, nor can it be predicted whether such variants having amino acid sequences with only one or two of such substitutions have the requisite binding activity. Moreover, many of the "combinatorial mutants", which are specifically encompassed by the claims, have not been shown to have the requisite binding activity, and undue and/or unreasonable experimentation would therefore be necessary before the claimed invention could be used, as it cannot be predicted whether these "combinatorial mutants" will have the requisite binding activity.

9. The rejection of claims 92 and 94 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "new matter" rejection.

At page 24 of the amendment filed June 14, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As explained in the preceding Office action, while the specification might arguably provide written support for a genus of antibodies and functional fragments comprising one or more CDRs having amino acid sequences that are substitution variants of those naturally occurring in monoclonal antibody HUIV26, which have or retain binding specificity for denatured collagen, such as at page 28, lines 18-21, it does not appear that the specification provides adequate written support for the claimed genus of antibodies and functional fragments produced by conservative substitutions within the CDRs, which have, per se, at least a 2-fold greater binding activity for denatured collagen, compared to the binding activity for native (non-denatured) collagen.

Again, the specification describes only two variants of monoclonal antibody HUIV26 having such preferential binding activity for denatured collagen, namely "2D4H1-C3" and "DhuG5"; see, e.g., Figure 8.

On the other hand, the specification does not appear to describe the members of the claimed genus as commonly sharing such preferential binding activity for denatured collagen, as again it only appears to describe the members as having or retaining binding specificity for a "cryptic collagen epitope" (see, e.g., page 28, lines 18-21).

For these reasons, claim 92 appears to introduce new matter, thereby violating the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

At page 13 of the amendment filed June 14, 2006, Applicant has asserted that support for the language of claim 92 is found in the specification, as filed, in, e.g., original claims 2, 21, and 22.

Claim 2 provides written support for a claim directed to an antibody or functional fragment thereof that has specific binding activity for a cryptic collagen epitope, wherein said antibody comprises one or more CDRs consisting of any of several specifically recited amino acid sequences; and claims 21 and 22 provide written support for a claim directed to an antibody or functional fragment thereof that has specific binding activity for a cryptic collagen epitope, wherein said antibody comprises a heavy or light chain,

respectively, comprising one or more CDRs consisting of any of several specifically recited amino acid sequences.

However, contrary to Applicant's assertion, none of claims 2, 21, and 22 appears to provide adequate written support for claims 92 and 94, which is drawn to a genus of antibodies or functional fragments thereof comprising a heavy and a light chain comprising one or more of the recited CDRs having conservative substitutions therein, which have, per se, at least a 2-fold greater binding activity for denatured collagen, compared to the binding activity for native (non-denatured) collagen.

This issue might be resolved if Applicant were to point to other particular disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the present claims.

10. The rejection of claims 89-100 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Beginning at page 21 of the amendment filed June 14, 2006, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As explained in the above rejection of the claims as lacking a sufficiently enabling disclosure, claims 89, 90, and 95-100 are directed to a genus of structural variants of monoclonal antibody HUIV26, which do not necessarily have or retain the binding specificity of the parent antibody. Because the members of the genus of antibodies and functional fragments thereof have no particular binding specificity or function, there is no correlation between any one particularly identifying (i.e., substantial) structural feature, which is shared by members of the claimed genus, and any one particularly identifying functional feature also share by at least most members of the genus. As a

consequence, the skilled artisan could not immediately envision, recognize or distinguish members of the claimed genus, and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Otherwise, as also explained in the "enablement" rejection, claims 91-94 are directed to a genus of antibodies, or functional fragments thereof, which are variants of monoclonal antibody HUIV26 having at least 2-fold greater binding activity for denatured collagen over native collagen. However, as explained in the preceding Office action, the specification, including the claims, as originally filed, does not appear to provide written support for such claims. As such, the specification does not adequately describe the claimed genus in such as way as to permit the skilled artisan to immediately envision, recognize or distinguish at least a substantial number of its members and thereby reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

For example, while the specification adequately describes the variant designated "2D4H1-C3" as having the requisite binding activity, no other member of the claimed genus, such as the elected species of invention, is so described[2]. Furthermore,

Contrary to Applicant's assertion, "2D4H1-C3", nor any other species of antibody described in the specification, is representative of the claimed genus, as a whole, particularly since there is no description of any one particularly identifying (i.e., substantial) structural feature, which is shared by any one species (e.g., "2D4H1-C3") and the other members of the genus, and any one particularly identifying functional feature also shared by that particular species and at least most other members of the genus.

Again, as noted in the preceding Office action, Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown

[2] Again, although "DhuG5" is described a variant of monoclonal antibody HUIV26, which has the requisite preferential binding activity for denatured collagen over native collagen, its structure has not been described; therefore, this species is not fairly representative of the genus.

in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of antibodies, which vary structurally and/or functionally, such that there is no correlation between any one particularly identifying structural feature and their common functional feature, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

Additionally, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). As explained in the above "enablement" rejection, the skilled artisan cannot predict the consequence of amino acid substitutions, especially within the CDRs of antibodies, upon their binding specificities and affinities. Moreover, the skilled artisan cannot predict which, if any of the claimed variants of monoclonal antibody HUIV26, including the elected species, have a specific binding activity for a cryptic collagen

epitope or at least 2-fold greater binding activity for denatured collagen over native collagen.

Furthermore, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, there is no language that adequately describes with the requisite particularity the genus of antibodies and functional fragments thereof having at least 2-fold greater binding activity for denatured collagen over native collagen. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

Again, as noted previously, the Federal Circuit has held that a generic statement that defines a genus *by only a common functional activity* does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997).

Applicant has remarked the Federal Circuit has recently decided that the description of a fully characterized molecular target of an antibody is sufficient to adequately describe an antibody that binds that target. See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC 2004). However, the same court decided that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)).

In this instance, claims 89, 90, and 95-100 are directed to a genus of structural variants of monoclonal antibody HUIV26, which do not necessarily have or retain the binding specificity of the parent antibody. Accordingly, in the case of claims 89, 90, and 95-100, it is not pertinent to ask the question, is the antigen to which the antibody binds a fully characterized antigen, as the antibody does not necessarily bind specifically to any particular antigen.

Otherwise, claims 91-94 are drawn to an antibody or functional fragment thereof that has a specific binding activity for a "cryptic collagen epitope" or has at least two-fold higher binding activity for denatured collagen over native collagen. Native collagen may be a fully characterized antigen; and were the claims directed to an antibody that binds

native collagen, perhaps the written description of an antibody that binds native collagen would be met by the description of the fully characterized antigen alone. However, in this instance, the claims are not directed to an antibody that merely binds its molecular target, but rather to an antibody that binds to a *cryptic* collagen epitope, so as to preferentially bind denatured collagen over native (non-denatured) collagen. The very fact that the epitopes to which the claimed antibodies and functional fragments thereof bind are cryptic suggests their nature is not fully characterized; moreover, because the epitopes reside on *denatured* collagen, it is submitted that they may not be characterized as having any uniform, constant or predictable structure.

Furthermore, it is aptly noted the specification does not describe with any degree of particularity a single member of the genus of "cryptic collagen epitopes" to which the members of the claimed genus of antibodies bind, such that the specification might reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed. At page 16, lines 9-13, the specification describes "a cryptic collagen site" or "a cryptic collagen epitope'" as "an epitope of a collagen molecule that is less accessible to binding of an antibody, or functional fragment thereof, in native collagen than in denatured collagen". However, given this definition of "a cryptic collagen epitope", one skilled in the art could not immediately recognize or distinguish members of the genus of claimed antibodies capable of binding such an epitope, because one could not immediately recognize or distinguish members of the genus of cryptic collagen epitopes to which the members of the claimed genus of antibodies must bind.

Again, as evidenced by Greenspan et al. (of record), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destablilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows the epitope to which

any given antibody binds can only be identified empirically. Even using a competition assay, the skilled artisan cannot determine whether an antibody binds the same epitope as another antibody because an antibody that competes with another does not necessarily bind the same epitope as the other; rather, one antibody may bind a spatially overlapping epitope to sterically hinder binding of the other. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of epitopes to which the members of the claimed genus of antibodies must bind, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of antibodies. Moreover, since the specification has not identified which amino acids of the genus of epitopes of the denatured collagen molecules to which the members of the claimed genus of antibodies must bind, which are critical or essential to the binding, one skilled in the art would not recognize that Applicant had possession of the claimed invention at the time the application was filed.

Finally, Applicant is again reminded the written description provision of 35 U.S.C § 112 is severable from its enablement provision. See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991); *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Conclusion

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
August 28, 2006